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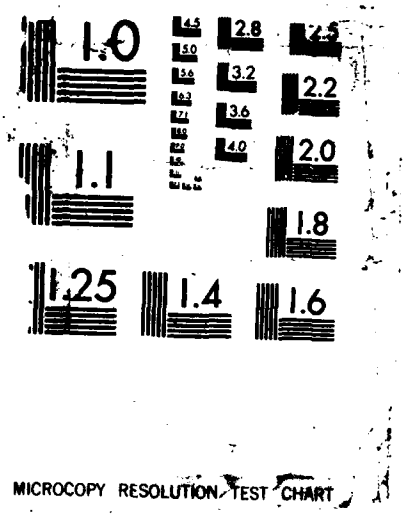
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MANAGEMENT OF HARD TISSUE AVULSIVE WOUNDS AND MANAGEMENT OF OROFACIAL FRACTURES

Annual Report

April 30, 1985

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-82-C-2168

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REPORT DOCUMENTATION PAGE

Form Approved
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1a. REPORT SECURITY CLASSIFICATION Unlimited	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S)	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION BATTELLE Columbus Laboratories 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code) 505 King Avenue Columbus, Ohio 43201	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION U.S. Army Medical Research & Development Command 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER DAMD17-82-C-2168
8c. ADDRESS (City, State, and ZIP Code) Fort Detrick, Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS PROGRAM ELEMENT NO. 62775A; PROJECT NO. 3S162, 775A825; TASK NO. AA; WORK UNIT ACCESSION NO. 044

11. TITLE (Include Security Classification)
(U) Management of Hard Tissue Avulsive Wounds and Management of Orofacial Fractures

12. PERSONAL AUTHOR(S)
Craig R. Hassler, Ph.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Annual Report	FROM 6/1/84 TO 4/30/85	1985, April 30	14

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)		
FIELD	GROUP	SUB-GROUP			
06	03		Bioceramics	Prosthethic Materials	Avulsive Wounds
06	02		Ceramic Implants	Implant Materials	Porous Ceramics
			Biomaterials	Maxillofacial	Calcium Phosphate

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The previous annual report dated May 31, 1984 on DAMD17-82-C-2168 indicated that two major difficulties had been encountered in trying to reproduce the required laminated tricalcium phosphate samples. This was especially frustrating since the previous materials had been successfully reproduced. One problem was the source calcium carbonate which is used as a starting product. The material originally used was no longer available. Several sources were evaluated until a satisfactory source was found. Extensive experimentation indicated that the method of manufacture of calcium carbonate drastically affected the ability to produce a high yield of tricalcium phosphate. The exact chemical nature of calcium carbonate differences was not ascertained due to project time and cost constraints. However, a commercial material was found which produced excellent results and allowed for nearly 100 percent yield of tricalcium phosphate.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION	
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS		
22a. NAME OF RESPONSIBLE INDIVIDUAL Mrs. Judy Pawlus	22b TELEPHONE (Include Area Code) 301-663-7325	22c. OFFICE SYMBOL SGRD-RMI-S

DD FORM 1473, 84 MAR 83 APR edition may be used until exhausted. All other editions are obsolete.

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A second problem identified was difficulty in properly sintering extruded layers together. This problem had previously been encountered and successfully overcome but was not reoccurring. Careful evaluation of the fabrication process indicated that the binder to ceramic ratio was more critical than originally thought and must be calculated and adjusted for each batch of material. Early in this project year, successful unidirectional tricalcium phosphate material was once again produced. Circular unidirectional ceramic implants 15 mm in diameter and 3-1/2 mm thick with 400 micron unidirectional pores and interconnections were produced. Omnidirectional random porosity materials with the same overall physical configuration were produced by the napthaline forming technique. These latter materials contained were to serve as historical controls. Both materials were supplied to the U.S. Army Institute of Dental Research (USAIDR) for surgical implant into experimental rabbit calvaria. These tests are presently underway at USAIDR. The basic hypothesis under test is that the unidirectional material will allow adequate ingrowth of bulk bone so that mechanical integrity of the repaired area will not be lost during the ensuing biodegradation of the tricalcium phosphate implant. Previous research on this project indicated that the loss of mechanical integrity was the major reason for failure when omnidirectional (random porosity) material was used. However, previous experiments with unidirectional materials indicated a successful transition to mostly bone without the loss of mechanical integrity. The samples presently under test at USAIDR are to substantiate advantages of unidirectional material as compared to omnidirectional material, previously observed in this laboratory.

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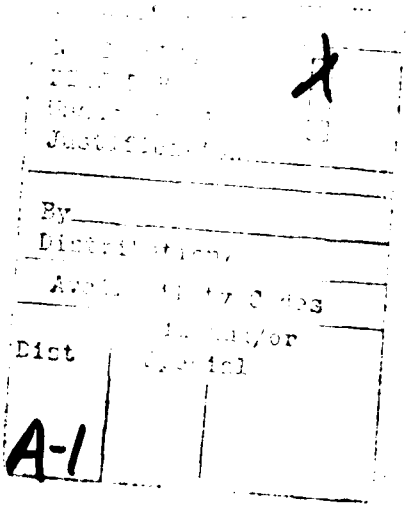
Biodegradable Ceramics
Bioresorbable Ceramics
Tricalcium Phosphate



SUMMARY

The previous annual report dated May 31, 1984 on DAMD17-82-C-2168 indicated that two major difficulties had been encountered in trying to reproduce the required laminated tricalcium phosphate samples. This was especially frustrating since the previous materials had been successfully reproduced. One problem was the source calcium carbonate which is used as a starting product. The material originally used was no longer available. Several sources were evaluated until a satisfactory source was found. Extensive experimentation indicated that the method of manufacture of calcium carbonate drastically effected the ability to produce a high yield of tricalcium phosphate. The exact chemical nature of calcium carbonate differences was not ascertained due to project time and cost constraints. However, a commercial material was found which produced excellent results and allowed for nearly 100 percent yield of tricalcium phosphate.

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FOREWORD

No animal research was conducted during this contract year. However, previously conducted studies adhered to the "Guide for the Care and Use of Laboratory Animals", prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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BACKGROUND, PROBLEM AND APPROACH

Historically, various techniques have been employed for the repair or treatment of osseous diseases, defects and wounds. Autogeneous bone grafting remains the most satisfactory approach, but is not without the disadvantages associated with double surgeries, limits in structural properties, and the limitations imposed on the repair of massive osseous defects.

Since April, 1969, Battelle's Columbus Laboratories has been conducting research under contract to the U.S. Army Institute of Dental Research (USAIDR), to develop resorbable ceramics for potential application in the repair of hard tissue avulsive wounds. The basic materials have been calcium phosphates. These materials were selected because they contain two of the essential elements of the natural bone mineral phase, calcium hydroxyapatite.

In vivo studies were conducted initially at USAIDR, using the sintered porous materials and slurries prepared at Battelle from tricalcium phosphate $Ca_3(PO_4)_2$ and other calcium orthophosphate powders $CaHPO_4$ and $Ca(H_2PO_4)_2$, to evaluate the potential use of calcium phosphates to both facilitate repair of bone defects and to determine the best material for future exploration[1-3]. The implant studies indicated that calcium phosphates consisting essentially of the mineral phases $Ca(PO_3)_2$, $Ca_3(PO_4)_2$, and $CaHPO_4$ are well tolerated by the tissue, appeared to be nontoxic, resorbable, and permitted rapid invasion of new bone.

Of the various porous calcium phosphate materials investigated, tricalcium phosphate, $Ca_3(PO_4)_2$, was selected for continued development and evaluation since it was easy to fabricate and was found to be both biocompatible and resorbable. Emphasis has been directed toward producing porous materials consisting of single-phase tricalcium phosphate[4-7]. Research on granular formations of tricalcium phosphates (TCP) continued at USAIDR. Basic research at Battelle-Columbus was focused on producing practical large segment replacement implants from TCP.

To provide basic resorption rate data on the *in vivo* behavior of solid tricalcium phosphate bioresorbable ceramics, implant studies were initiated in 1975 at Battelle-Columbus using the rabbit calvarium model[8]. Early samples of tricalcium phosphate were implanted as a control and samples

to two new materials were implanted for comparative observation. These new materials were prepared using improved processing techniques derived in previous materials development studies and represented significant improvements in the structural characteristics of porous tricalcium phosphate. The characterization of the materials involved and the results of the *in vivo* studies were the subject of the fifth report[8].

These results indicated that the improved material exhibited significant increases in resorption rate. In fact, the material resorbed so rapidly that after the ninth month the implant appeared to be granulated and was invaded with connective tissue. This result does not imply lack of biocompatibility, but does suggest that such rapid degradation can be deleterious in stress-bearing situations.

To determine the effects of structural variations on resorption rate, experimental porous implants were prepared using a single tricalcium phosphate power with different pore size distribution. Three materials were prepared for *in vivo* evaluation. These studies demonstrated that orientation of pore structure is a more important variable than pore size distribution[9]. The study indicated that a higher density material of the stoichiometric chemistry with directional porosity is probably the desired material.

The seventh report[10] demonstrated that the concept of directional porosity could provide a satisfactory result; adequate ingrowth of bone to provide mechanical integrity prior to loss of mechanical integrity of the tricalcium phosphate. These results were corroborated by Tortorelli[11]. The material used in these experiments was far from ideal; consequently, a better method of production was sought. The eight report outlines the development of a better material, the second generation material, and early phases of its *in vivo* evaluation[12]. The ideal material should minimally inhibit the ingrowth of bone; consequently, large pores and a high pore density are desirable. The ideal material should also be of high strength and should have mechanical properties approaching bone. Consequently, a material of high density in the non-porous regions was sought. It was also deemed desirable to have a material that could be readily manufactured with the pore alignment and size required for a particular application.

The Annual Report dated May 19, 1983[13] contains the completed animal evaluation of the material previously placed in test. The circular unidirectional material samples implanted in rabbit calvaria exhibited considerable biodegradation especially in months 9 and 12. Most important, there was no loss of mechanical integrity. Mature remodeled bone was found completely through the large porosities transversing completely through the implanted material. The pores had increased in diameter in the overall tricalcium phosphate specimen had decreased in size thus indicating substantial biodegradation. At the end of 12 months, some tricalcium phosphate material remained: it had been predominately replaced with bone. Non-implanted control sites left vacant contained only fibrous tissue ingrowth thus indicating a defect of the diameter utilized in these experiments would not naturally full with bone.

On the strength of these in vivo evaluations, research was geared towards further improving the mechanical integrity and quality of the unidirectional implants. Unfortunately, two major draw backs inhibited progress in 1983 to 1984. Difficulty was obtained in producing a high yield of tricalcium phosphate. This problem was eventually solved and it was determined that the method of manufacture of the source calcium carbonate was critical to successfully yield of tricalcium phosphate. Further, difficulties were encountered in obtaining interlaminar bonding of the extruded layers. This problem was eventually traced to an incorrect binder to ceramic ratio. An excesssive layer of binder material apparently migrated to the surface of the extruded pieces and prevented proper fusing upon sintering. The present research was directed towards understanding and correcting this problem. This problem was especially frustrating since high quality material had been previously produced by this same method which now was not producing satisfactory material.

MATERIALS AND METHODS

The proper method to determine binder to ceramic ratio is known as the Critical Powder Volume Concentration Test or CPVC. The CPVC is based upon the ASTM D-281-31 oil adsorption test, where an oil is mixed

into a powder and the torque required to maintain a preset mixing speed is measured. The point at which the maximum torque occurs is identified as CPVC. CPVC is related to the optimum binder concentration required for hot extrusion. This test was performed on the tricalcium phosphate material produced in 1982, but inadvertently not performed on the 1983 produced TCP. The results of the CPVC for the 1982 and 1983 TCP are:

	1982	1983
CPVC (volume %)	64	61
TCP (weight %)	86.3	84.8
Oil (weight %)	13.7	15.2

The 1983 TCP was extruded with 13.7 weight percent organics while the CPVC test indicates that the 1983 TCP required 15.2 weight percent organics. This is a significant difference. Either insufficient or excess binder could result in binder migration, formulation of large voids or segregation of the coarse and fine ceramic particles. Any of these events could hamper sintering or bonding of the layers.

Bonding of the layers was significantly improved by the following procedures: (1) removing (sanding with 600 grit) .254 mm (.01") of material from both sides of every layer, (2) coating with camphorated cottonseed oil, (3) burnout of the organics at 5°C/hour to 500°C, (4) sintering at 1100°C for 2.5 hours. Two separate experiments were performed. The first experiment contained three samples, each two layers thick. The second experiment contained 6 samples each two layers thick. All samples were bonded but with force all could be separated. Earlier in this program, samples without the sanding operation but processed similarly either did not bond or bonded slightly. This experiment reinforces the CPVC test result that the system had the wrong concentration of binder.

Apparently the small differences in CPVC volume are critical. Consequently, for all subsequent batches, CPVC was calculated and determined for each batch of material produced. All the parameters of the extrusion subsequent calendering, stacking, burnout, and sintering remained the same as previously reported. A successful material was immediately produced

thus validating the hypothesis that CPVC was critical. As the CPVC decreases the weight percent volume of tricalcium phosphate decreases. Thus, the materials that were unsuccessful had slightly lower tricalcium phosphate percent weight and slightly higher organic concentrations. The additional concentration of organics was apparently adequate to interfere with the burnout and sintering procedure by migrating to the edges of the work pieces during the extrusion technique. It was determined that the CPVC for each batch should be adjusted to 64 so that the organic binder percentages remains at 13.7 percent and the tricalcium phosphate at 86.3 weight percent.

Some slumping of unidirectional pores was noticed in samples where the diameter of the solid material between the pores was equal in volume to the void area. In an attempt to minimize slumping every third groove was removed from a calendering tool and a new tool was produced in which approximately 40 percent more structural material was left between each pore, thus the number of pores per unit area was slightly decreased. Experimental sintering was performed utilizing work pieces produced with an original calendering tool plus the two modified tools designed to leave more supporting material between the pores. Of these three techniques the modified tool which left 40 percent more material between the pores produced the most satisfactory results. The above mentioned manufacturing techniques were utilized to provide experimental specimens, 15 millimeters in diameter and 3-1/2 millimeters thick.

Further, samples of tricalcium phosphate omnidirectional (random porosity) were produced of identical size to the omnidirectional samples to serve as historical controls. All materials were transmitted to USAIDR in late July for subsequent animal experimentation.

ANIMAL EXPERIMENTATION

A research protocol was prepared by Dr. Jeffery Hollinger, Chief of the Physiology Branch, USAIDR. The purpose of the study was to ascertain the quality of ingrowth into the tricalcium phosphate material placed in rabbit calvaria to further determine if more favorable ingrowth is obtained with the unidirectional specimens, and if integrity can be maintained with unidirectional implant materials.

The material supplied to USAIDR was a third generation of the unidirectional technology. This material had improved strength characteristics and was especially better in the interlaminar bonding characteristics.

Experiments are now nearing completion in the USAIDR laboratories under the direction of Dr. Hollinger. Verbal reports on 6 month physiological analysis indicate preferential ingrowth of bone into the uni rectional specimens. At the time of this report, further analysis of subsequent animals to the evaluating the 12 month was not available.

CONCLUSIONS

This year's research resolved the problems inhibiting successful manufacture of a unidirectional tricalcium phosphate. A successful product was produced in research quantities and subsequently implanted into rabbits at USAIDR. These experiments appear to be proceeding satisfactory but definitive information as to the ultimate success of the material has not yet been obtained. These results should be available in late summer of 1985.

RECOMMENDATIONS

It is recommended that a complete analysis of the animal studies be performed to reconfirm the advantages of a unidirectional biodegradable material. If the previous experiments are reconfirmed (the unidirectional material) provide superior results in terms of ingrowth and maintenance mechanical integrity, the material should be further investigated for use in numerous dental and orthopaedic applications.

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